CLAIMS

1. A method for imparting resistance against collapsing to contrast agents for ultrasonic echography which consist of gas-filled microvesicles in suspension in aqueous liquid carrier phases, i.e. either microbubbles bounded by an evanescent gas/liquid interfacial closed surface, or microballoons bounded by a material envelope, said collapsing resulting, at least in part, from pressure increases effective e.g. when the said suspensions are injected into the bloodstream of patients, said method comprising forming said microvesicles in the presence of a gas, or if the microvesicles are already made filling them with this gas, which is a physiologically acceptable gas, or gas mixture, at least a fraction of which has a solubility in water expressed in liters of gas by liter of water under standard conditions divided by the square root of the molecular weight in daltons which does not exceed 0.003.

2. The method of claim 1, which is carried out in two steps, in the first step the microvesicles or dry precursors thereof are initially prepared under an atmosphere of a first gas, then in the second step at least a fraction of the first gas is substantially substituted by a second gas, the latter being said physiologically acceptable gas.

3. The method of claim 1, in which the physiologically acceptable gas used is selected from $SF_6$, $SeF_6$, Freon® such as $CF_4$, $CBrF_3$, $C_4F_8$, $CClF_3$, $CCl_2F_2$, $C_2F_6$, $C_2ClF_5$, $CBrClF_2$, $C_2Cl_2F_4$, $CBr_2F_2$ and $C_4F_{10}$.

4. The method of claim 2, in which the gas used in the first step is of a kind that allows effective control of the average size and concentration of the microvesicles in the carrier liquid, and the physiologically acceptable gas added in the second step ensures prolonged useful echogenic life to the suspension for in-vivo ultrasonic imaging.

5. The method of claim 1, in which the aqueous phase carrying the microbubbles contains dissolved film-forming surfactants in lamellar or laminar form, said surfactants stabilizing the microbubbles boundary at the gas to liquid interface.

6. The method of claim 5, in which said surfactants comprise one or more phospholipids.

7. The method of claim 6, in which at least part of the phospholipids are in the form of liposomes.

8. The method of claim 6, in which at least one of the phospholipids is a diacylphosphatidyl compound wherein the acyl group is a $C_{16}$ fatty acid residue or a higher homologue thereof.

9. The method of claims 1 and 2, in which the microballoon material envelope is made of an organic polymeric membrane.

10. The method of claim 9, in which the polymers of the membrane are selected from polylactic or polyglycolic acid and their copolymers, reticulated serum albumin, reticulated haemoglobin, polystyrene, and esters of polyglutamic and polyaspartic acids.

11. The method of claim 1, in which the forming of the microvesicles with said physiologically acceptable gas is effected by alternately subjecting dry precursors thereof to reduced pressure and restoring the pressure with said gas, and finally dispersing the precursors in a liquid carrier.

12. The method of claim 1, in which the filling of the microballoons with said physiologically acceptable gas is effected by simply flushing the suspension with said gas under ambient pressure.

13. The method of claim 1, which comprises making the microvesicles by any standard method known in the art but operating under an atmosphere composed at least in part of said gas.

14. Suspensions of gas filled microvesicles distributed in an aqueous carrier liquid to be used as contrast agents in ultrasonic echography, characterized in that the gas is physiologically acceptable and such that at least a portion thereof has a solubility in water, expressed in liter of gas by liter of water under standard conditions, divided by the square root of the molecular weight which does not exceed 0.003.

15. The aqueous suspensions of claim 14, characterized in that the gas is such that the pressure difference ΔP between those pressures which, when applied under standard conditions and at a rate of about 100 Torr/min to the suspension cause the collapsing of about 75%, respectively 25%, of the microvesicles initially present, is at least 25 Torr.

16. Aqueous suspensions according to claim 14, in which the microvesicles are microbubbles filled with said physiologically acceptable gas suspended in an aqueous carrier liquid containing phospholipids whose fatty acid residues contain 16 carbons or more

17. Contrast agents for echography in precursor form consisting of a dry powder comprising lyophilized liposomes and stabilizers, this powder being dispersible in aqueous liquid carriers to form echogenic suspensions of gas-filled microbubbles, characterized in that it is stored under an atmosphere comprising a physiologically acceptable gas whose solubility in water, expressed in liter of gas by liter of water under standard conditions, divided by the square root of the molecular weight does not exceed 0.003.

18. The contrast agent precursors of claim 17, in which the liposomes comprise phospholipids whose fatty acid residues have 16 or more carbon atoms.

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